A Case of Fatal Seizure and Unconsciousness Caused by Panipenem/Betamipron

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Introduction

It is recognized that antibiotics which contain β-lactam; penicillins, cephalosporines and carbapenems (imipenem/cilastatin, panipenem/betamipron and meropenem etc.) cause seizures as adverse effects1)−5). The presence of the open β-lacam metabolite was reported to inhibit the binding of the inhibitory neurotransmitter, gamma aminobutyric acid, to its receptor in the central nervous system (CNS), and exert a CNS stimulatory effect6).

Several factors have been identified as predisposing conditions to the neurotoxicity: (1) excessive dosage, (2) renal insufficienty, (3) a pre-existing CNS disease such as a cerebrovascular accident, tumor, menigitis, head injury as well as a pyevious history of seizures, and discontinuation of anticonvulsant therapy and (4) pseudomonas aeruginosa infection1)−5).

Seizures due to carbapenems, mainly imipenem/cilastatin, were reported to occur in 2-3% of the patients1)−5), and a more recent study reported an incidence as high as 10% in selected populations7). Panipenem/betamipron has been manufactured and sold only in Japan for 4 years, and more than 20 patients with adverse effects of seizures were reported by the manufacturer according to a report for the Ministry of Health and Welfare8). Seizures due to carbapenems are usually transient and irrevers-ible, and no fatal cases had been reported1)−8).

Here we report a case of fatal seizures and unconsciousness caused by panipenem/betamipron in an elderly patient with malnutrition who had potential cerebral disease and renal failure, although the latter two factors were not apparent on admission.

Case

An 84-year-old woman complained of general fatigue, anorexia and disorientation in September 1997. She noticed lymph node swelling in September 1993, and was diagnosed with non-Hodgkin’s malignant lymphoma, but was not treated. The physical findings on admission on November 7 were hight 140 cm, body weight 35 kg and marked anemia and edema. The laboratory findings on admission are shown in Table 1. The patient complained of fever and a chest X-ray revealed pneumonia and pleural effusion of the right lung. Computed tomography (CT) did not reveal progression of lymphoma. Cytological and bacteriological examinations of the pleural fluid did not reveal any abnormal cells or bacteria. The patient was administered panipenem/betamipron, 0.5 g in 100 ml of saline, by drip infusion for an hour, twice on November 8, and that night she suffered from seizures of the face and extremities followed by unconsciousness and coma. The 24-hour creatinine clearance

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Table 1  Laboratory findings on admission.

<table>
<thead>
<tr>
<th>CBC: RBC</th>
<th>210 × 10^6/μl, Hb 5.6 g/dl, Ht 19.0 %, platelets 19.9 × 10^4/μl, WBC 3,700/μl (N Seg 68%, Eo 1%, Lympho 16%, Mono 15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry:</td>
<td>CRP 17.5 mg/dl, total bilirubin 0.7 mg/dl (direct 0.3 mg/dl), serum protein 4.9 g/dl, albumin 2.1 g/dl, globulin 2.8 g/dl, GOT 14 IU/l, GPT 11 IU/l, LDH 386 IU/l, cholinesterase 0.26 αₕH, γ-GTP 14 IU/l, alk phos 180 IU/l, glucose 149 mg/dl, cholesterol 139 mg/dl, BUN 17.1 mg/dl, creatinine 0.6 mg/dl, uric acid 4.0 mg/dl, Na 148 mEq/l, K 2.8 Cl 92 mEq/l, Ca 8.9 mg/dl, P 2.1 mg/dl</td>
</tr>
</tbody>
</table>

on the following day was 59.4 l. A brain CT did not reveal hemorrhage or infarction, and only atrophy was observed. The seizures were treated with diazepam and phenytoin, and penipenem was discontinued. The patient remained unconscious, ranging from coma to stupor until death. EEG examination on November 11 and 14 revealed frequent sharp and slow waves in the left hemisphere and phase reversal was observed on the left antero-temporal regions. Spinal fluid examination revealed normal pressure, no pathological cells, and normal biochemistry, and was negative for HSV DNA. Serological tests for HZV, HSV and CMV were negative. The patient was further treated with phenytoin and carbamazepine, and the doses were adjusted within the therapeutic plasma ranges by measuring their concentrations. BUN and creatine levels gradually increased, to a maximum of 131 mg/dl and 5.5 mg/dl respectively, and the patient died of renal failure on December 5.

Discussion

Our patient had risk factors for neurotoxicity of panipenem/betamipron in that she was aged and had malnourished. Although due to disorientation by dementia and brain atrophy were observed by CT, the patient had no apparent underlying cerebrovascular disease or renal failure on admission. Seizures usually occur beginning 7 days after administration, are usually transient and reversible after discontinuation of antibiotics and are easily controlled by anticonvulsants. The seizures in our patient occurred 1 day after administration of panipenem/betamipron and were followed by unconsciousness and death. There have been no other reported fatal cases. The reason with unconsciousness continued is unclear; however, an epileptogenic EEG was observed even 1 week after the initial seizures.

Impaired renal function is the most important physiological effect of aging. It may caused decreased clearance of antibiotics, increased plasma levels and half-life, increased permeability of the blood brain barrier and increased penetration of antibiotics into the CNS. Even while maintaining normal concentrations of creatinine and blood urea, the elderly show decreased creatinine clearance as was observed in the present case, on the day following the seizures, which is of major importance in the elimination of β-lactam antibiotics. Reduced binding of antibiotics due to the reduced serum concentration of albumin, as in the present case, may also result in increased free pharmacologically active drug and increased plasma and brain tissue levels of antibiotics. Low body weight is a factor in overdosage of antibiotics and was observed in ours case. In addition, an electrolyte imbalance, such as hypopotassemia, which was observed in our case, was also reported as a risk factor for seizures.

In penicillins and cephalosporines, an open β-lactam ring was found to be essential for evoking seizures, however, in carbapenems the ring was not necessary to evoke seizures, but the presence of the amino group in the C-2 side chain was important and its degree of basicity was correlated with the activity. Although cilastatin could cause seizures when given intraventricularly to animals, the
large amount needed suggests that it would not cause seizures in clinical situations\(^9\). Imipenem is reported to bind to gamma aminobutyric acid receptors with greater activity and is more frequently associated with seizures than other β-lactam antibiotics\(^9\). Among carbapenems, imipenem was found to have the strongest ability to evoke seizures, while panipenem had half of that activity and meropenem had no activity according to a study of ventricular administration of antibiotics\(^6,9\). The seizures in our patient may have been caused by a mixture of the various risk factors.

These results indicated that panipenem/betamipron may cause seizures, sometimes with a fatal outcome. The patients with adverse effects of seizures will increase when the number of patients administered panipenem/betamipron increase. Special attention should be paid to the risk factors regarding neurotoxicity when administering carbapenems, especially to aged patients who are likely to have potential cerebrovascular, or renal disturbances, low body weight and malnutrition. In patients who require the drug, the dose should be adjusted to the patient's clinical status according to the guidelines for dosage\(^1\)–\(^5\).

References


Panipenem/betamipron (PAPM/BP) による致死的な痙攣
および意識消失を起こした 1 例

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要旨

症例84歳、女性が全身倦怠感、食思不振、失見当識を主訴として来院した。入院時の諸検査では貧血、低アルブミン血症、低体重、浮腫を認めたが明らかな腎障害は認めなかった。合併した肺炎に対してPAPM/BPの投与を行った当日に全身の痙攣および意識消失が起こった。翌日のクレアチニンクリアランスでは障害を認めた。脳CTで萎縮以外は明らかな血管性病変は認めなかった。痙攣発作は抗痙攣剤の投与により抑えられたが、脳波では依然として棘および徐波の頻回の出現を認めた。意識消失は29病日に腎不全にて死亡するまで持続した。高齢者におけるカルパベネム系の抗生剤の投与に際しては神経毒性に対する危険因子に注意する必要がある。

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